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# A STUDY OF CEREBROVASCULAR CHANGES AND CEREBRAL EDEMA.

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Ram D 692.
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C O N T E N T S .



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# I N T R O D U C T I O N .

The importance of cerebro-vascular changes, accompanying cerebral edema , has been widely recognized. For the observation of these changes, a subtle method allowing continuous registration was thought to be most appropriate and the concentrated effort of many was directed to develop such a method. This method should at the same time be entirely harmless and by itself should not influence cerebral hemodynamics. While serial angiography ( in clinical medicine) certainly allows in certain instances to diagnose localized ( e.g. temporal lobe ) edema, it by itself changes cerebral hemodynamics enough to cause temporary clinical manifestations which - it is generally assumed - are due to these influences on the vascular changes.

To approach the goal of a method such as was referred to above various investigators followed several lines of studies. Soon after the first preliminary results of the project on Rheoencephalography - initiated by the principal investigator about a decade ago - were obtained, it was felt, that these results pointed to a promising line of investigations, which were at that time thought to be very promising . In fact, the results obtained over the years not only fulfilled the hopes and promises of the early steps of the development of this technique, but surpassed all hopeful thoughts in providing records at the occasion of experimental and clinical investigations, which proved that this method was applicable to any problem of cerebral hemodynamics.

This method represents an indirect, electrical method using the known fact of changing electrical resistance ( impedance ) to alternating current with circulatory events. Using various frequencies

and varying circuit d[illegible]ms, several authors gave various names to techniques destined to allow the observation of changes in hemodynamics of several parts of the body on a long term basis, i.e. continuously. In studying these attempts it soon became evident to the principal investigator that a standardization was urgently needed to achieve a base line for comparison. Applying the investigations of theoretical physicists to the problem at hand, an apparatus was selected and with minor changes adapted to allow the application to the project of following cerebro-vascular changes continuously. Two specially adapted Wheatstone bridge arrangements were used together with electronically arrived at derivatives to present records which had to be tested for: consistency, reproducibility, applicability to problems of intracerebral in contrast to over-all-cranial ( intra and extra-cranial!) circulation. All these questions have been solved and answered conclusively in favor of the rheoencephalographic technique ( abbreviated as REG ). Various known influences on the cerebral circulation had been studied by REG and it could be shown that the operative procedure of a trephination did not alter the record obtained( see FTR/R+D311 ). Production of experimental cerebral edema ( localized ) by more than one method to compare the effects of procedures from the REG - and of course also histological side had been performed and the results compiled tabulary and pictorially ( see FTR/R+D 447 ) together with synchronously recording blood pressures .

These studies together with the clinical testing of the method as well as application to some very important aspects of diagnostic medicine ( such as the differentiation of cerebral contusion from cerebral compression of all forms, harmless procedure to rule out or confirm objectively any postop.hemorrhage after a craniotomy ( if suspected on clinical grounds ) where one might hesitate to perform angiography;

simple diagnostic help in cases of cases of a.-v. shunts in cerebro ; carotid occlusion ; additional diagnostic help in cases of cerebro-vascular insufficiency and the like ) - all these results could only confirm very validly the opinion held at the beginning that there is a method at our disposal from which we may expect some solution of experimental,as well as clinical problems unsolved so far. But we must invest intensive work and study to this method . That investigations of REG is not waste of time and energy was proven by results obtained so far.

Application of the REG to the study of vascular factors of cerebral edema has yielded some interesting results from a very general point of view. One of them has been specially stressed and reported as part III of FTR/R+D 447. Others will be touched in this FTR. The apparatus used has behaved very well, but the one problem of eliminating manual control ,which seems most important a feature to the principal investigator , could not be solved satisfactorily. The very simple elimination of equilibration of the Wheatstone Bridges by very carefully balancing the bridges at a certain mid-point, as apparantly is the case with several aparatus available commercially , does not seem the solution of choice. The importance of obtaining an exact balance of the bridges should not be underestimated and can not be overestimated. Several otherwise quite serious minded persons,known to the principal investigator , could not arrive at satisfactory recordings ( nothing to say of the relevant clinical and experimental proofs only obtainable by appropriately recorded tracings ) only because of "grossly underbalancing " their bridges.

In this connection brief mention must be made of the general impression, the principal investigator had while attending the Winter Meeting of the European EEG- Societies. There, a whole day was dedicated to discussions of REG. One group of authors calling their method (which entirely deviates in principle and results from REG) Rheography II was presenting some preliminary results. These results were questioned by a well known French neurophysiologist and this scientist also could point out some misconceptions behind the basis of this method. The basis of this method is picking up differential potentials from the scalp with separate electrodes while the current carrying electrodes are placed bitemporally. This already shows that the name Rheography is not applicable to the method . The principal investigator - at a time - suggested the name"Differential Potentiometry"or " Differential Potentiogram" to this other method. After looking at various experimental and clinical REG-tracings, this same French neurophysiologist entirely backed the theoretical principle and concept of Rheoencephalography as used in this study. A great number of visiting Neurosurgeons, Internists and other specialists from practically all over the world could observe the reproduceability and steady performance, as well as application to some critical clinical problems while trying to familiarize themselves with Rheoencephalography. In contrast to this, it is known to the principal investigator, that one publication on the so-called Rheography II in the English language contains a statement entirely wrong.

Returning to the REG, and the statement on the last missing link in observations of experimental cerebral edema and REG (see FTR/R+D 447,pg 4,paragraph 3 of I),these studies were continued and results of all methods used

were compared in all possible aspects. The section on Abstracts of Results now following will give an outline of the results and steps of investigation as carried out during this reporting period. Next, there will follow the presentation of the results, followed by a section on discussion of the results. An administrative note and an appendix, containing (A) tabulary and (B) pictorial matter concludes this report.

## A B S T R A C T of R E S U L T S .

During the reporting period (March 1 1962 - Sept.30,1963; actual period see under Administrative Note ) 268 animal experiments were performed, 43 control runs were made for which 79 animals were used. All animals had to be sacrificed. The manner of anaesthesia was, as usual, with intraperitoneal Pentothal, 50 mg/kg of body weight. There was one anaethetic death. The animals were grouped according to the type of experiment planned. During the first 3 quarters of the reporting period, some animals were used for more than one (sometimes 4 ) studies, during the last quarter, most animals - due to the type of experiment - could only be used for one experiment.

After a sufficiently large number of experiments using the sudden decompression technique of producing experimental cerebral edema, the technique of temporary occlusion of the carotid artery, thought to be the most physiological one , was extensively studied. Two ways of preparing the animal (see under results) were executed. This method of production of cerebral edema led to partial or complete occlusion of the respective carotid artery in 7 animals. REG-evidende of this is shown.

Respirations were occasionally recorded synchronously. Three dogs were used for CSF-pressure studies. No appearent change of CSF-pressure with any one of the three relevant methods of production of cerebral edema was observed.

Setting the resistive and capacitive parameters of the REG-adjusting and equilibrizing instruments to average values did not produce reproduceable tracings, on the contrary; even though the differences of resisitive and capacitive settings of the apparatus do not vary extensively from animal to animal, it became apparant, that even small changes of setting change the tracings rather markedly. It was observed, that these changes are not as marked in human subjects, but differences are present also there.

Finally, the special observation (see FTR/R+D447) was amended by pressure studies.

## P R E S E N T A T I O N of R E S U L T S .

To supplement the number of experiments for production of cerebral edema , temporary occlusion of one carotid artery was used as the third method. Besides, the number of experiments testing the effect of drugs (injected or inhaled) on REG before and after the sudden deflation technique of producing cerebral edema was brought to a number comparable with the previous method.

Two methods of preparing the carotid artery for intracarotid injections in case of testing the temporary occlusion method on its effect were used. In one

a branch of the carotid artery was approached, a catheter inserted against the direction of the stream of blood and tied securely in place, but in a way, that the catheter did not obstruct the lumen of the carotid artery. Then only, the control-REG was registered and temporary occlusion was effected under continous REG-control. In several instances, surgical approach to the carotid artery, clamping(temporary) and closure of the wound was done one or more days prior to inserting the catheter into a branch of the carotid. At the end of the experiment, the small branch was ligated, and the carotid was left undisturbed. The animal was ready for another experiment without intracarotid injection.

The observation of partial or complete obstruction of a carotid artery after this procedure of temporary occlusion in several animals made the observations on other than intracarotid application of drugs invalid in those animals because of the carotid occlusion. When there was no REG-evidence of obstruction, no such occlusion was found on autopsy of the animal. However, for a repetition of those studies, done on animals with beginning carotid obstruction, no chance of obtaining another obstruction was taken. Instead of cannulating a branch of the carotid, the controll-REG was recorded after surgical exposure of the carotid artery. Next, the temporary occlusion of the artery was used to split the wall of the artery longitudinally and insert a T-typed tiny tube with a catheter of relatively large size attached to the free end. Tying the T-tube in place was effected in less than 10 seconds. Now, the temporary obstruction of the blood flow through the carotid artery was removed and during all this time, REG-tracings were taken. With this technique, each animal could only be used once ,but intracarotid injections (or other applications of drugs) could be combined with intracarotid arterial pressure recordings, due to the now very much larger lumen of the catheter.

As evidence for the occurence of carotid obstruction, figures 1,2 and 3 are shown.

From the testing of various injections or inhalations ($N_2$,fig.8) to observe changes in cerebral hemodynamics following experimental cerebral edema as compared to the same tests without one-sided edema, several examples are given as figures 4 (i.v.injection of caffeine, also evidence of lowering of blood pressure without changes in REG), 5 (n-adrenaline, intra-carotid injection) and 6 (i.v. injection of aminophylline, after exper.edema, also an example of decreasing REG-amplitude with falling blood pressure). Results were similar to or identical with the two other procedures used to obtain unilateral cerebral edema. A tabulary summary of all three methods is given in Appendix (A).

Only with caffein and aminophylline the results were somewhat different than with the two other methods of production of experimental cerebral edema and this is shown in figures and will be discussed in the next section. Another figure shows the composite figuration of pressure recordings in supplement of the special observation referred to earlier. Several drugs were tested and the optimal effect of an experimental drug, having no effect neither on pressure nor REG in a control injection is shown here as it concerns the pressure. This seems justified because the drug mentioned in the earlier report does have no REG, but an average pressure effect on control runs which does not seem insignificant.

Also in the tabulary survey of Appendix (A), the experimental average of those settings is given, which were observed to occur most frecuently in adjusting the rheograph ( resistive as well as capacitive settings of dials). As it was already mentioned earlier, taking these values as presetting on a number of experiments did not produce tracings identical with the individual setting.

It is held important that each adjustment of the bridges is individually done to provide conditions for comparison because of reproduceability which is achieved then. The implications of this have already been mentioned: it is the necessity of having automatic equilibration rather than optimal balancing in the construction of the bridges without the possibility to equilibrize . Therefore, the necessity for automatic equilibration is stressed. It is not held necessary to produce tracings for this argument.

## D I S C U S S I O N of R E S U L T S .

The results of the experimental production of cerebral edema by three different methods, as presented in summary in Appendix (A) and the results of various testing before and after the production of experimental cerebral edema by the named three methods as presented again in Appendix (A) speak for themselves. No further elaboration is necessary. There are no criteria which allow from registration alone without a control run to specify the occurence of cerebral edema. But in certain instances, with a control run, the suspected presence of cerebral edema may be supported. Without other indications, the presence of or coming about of cerebral edema may be suspected. Various tests, those most reliable indicated by an asteric in the tables of Appendix (A), may be used to substantiate the presence of cerebral edema. Clinical implications of this finding , which have not been touched in this report, could be cited and would certainly substantiate the validity of projecting the results of this experimental study on human pathological states. Of course, no normal persons have been subjected to edema - producing manoeuvers.

The only point that is to be mentioned here is the difference in reaction shown to the test injection of caffein and aminophylline with the third method of production of experimental cerebral edema, temporary occlusion of the carotid artery. The only explanation on hand would seem to be that caffein either dilates or constricts the vessels depending on(apparently) the vegetative state of the vessels at the start of the experiment. In partially stimulating the carotid plexuses with instrumental while temporary occluding the artery may rest the mechanism which causes the different reaction as is shown in the tabulation of Appendix (A). The same explanation may well hold for the reaction of REG to aminophylline, of which the direct action on cerebral vessels and on general systemic blood pressure are somewhat in contrast to each other.

The other point which must be mentioned in this discussion is the already mentioned discrepancy in the tracings obtained with average settings of the bridge and initial equillbration at the start of each experiment. Since the automation is of prime concern to the principal investigator, even though the manufacturer of the instrument denied the possibility to have automation of the equilibration truely contained in a reasonably small apparatus, the opinion of three physicists and theoretical electronics engineers(not in business) was obtained separately from each other. In the opinion of these serious people, there should be a possibility to incorporate true equilibration(fully automatic)with miniaturization in an arrangement that equals the circuit of the machine used. There also should be the possibility to automatize the evaluation of tracing. In one or the other more important point after automatic balance is achieved: this was the answer of one of the thre persons to the specific question of the principal investigator.

It therefore seems that the basic concept and the future development, as seen by the principal investigator are basically sound and attainable.

## A D M I N I S T R A T I V E  N O T E .

There occured no changes in personnel during the reporting period. There were no changes in any policies by the contractor.

The research group consisted of the principal investigator, who during this reporting period was appointed to "Dozent" of this University and acclaimed a member of the"International College of Surgeons", Austrian Chapter; a physician; a chemist (Ph.D.); a laboratory technician and a secretary. For this project, the members of the group spent a total of just over 6.4oo manhours to perform 268 animal experiments and 43 control runs. For this number of experiments, 79 animals were used. All this ammounted to 8o % of the contract expenses. Other costs included: recording paper, drugs, animal food and the usual laboratory and office expenses ( 9% ), depreciation of equip,ent (EEG-apparatus: 8 % ) and various repairs (including part of cost of pressure recording channel repair: 3 % ).

The contract was supposed to require the onset of work on March 1,1962. Due to essential adjustments of the working site, postponement of this date could be obtained and the contract was accordingly amended. Work began on July 1,1962. During the third quarter of the working period, the pressure channel began to perform badly and amplification decreased to a point, where work with this essential part had to be interrupted. According to the advice obtained, the studies were interrupted until the channel was successfully repaired and controls indicated the proper performance. This led to another 3-months delay of the progress of the project and the reporting period of the last quarter was July 1 to September 3o,1963. ( instead of April-June of the same year). During the three-months interruption from April to end of June, only animal experiments without pressure recording were done during the first three weeks of April and discontinued until the pressure channel was obtained back during the third week of

June. During the last week of June, the extensive testing of the repaired channel was carried out. In the meantime, calculations of REG-settings for resistive and capacitive values were obtained to make use of these data during an interval during which more time for this was available than when animal experiments were carried out.

Papers having appeared in print or being in various stages of printing or preparation are:

Influence of experimental cerebral compression on cerebral circulation (Die Beeinflussung der Hirndurchblutung durch experimentelle Compressio Cerebri; Klin.Med.18:187-193,1963. In German. English abastraction obviously not necessary, because it is an elaboration and extension of work presented in Washington ,D.C. 2 yrs ago. After a paper presented almost 1 and 3/4 of a year ago at a Meeting of the Astrian Surgical Association.)

Cerebral fluid enzyme studies in closed head injuries.(Printed so far only as short abstract)

The diagnosis and treatment of intracranial a.-v- shunts.

An adjuvant in the early diagnosis of cerebral arteriosclerosis: The Rheoebcephalogram.

Nature and Therapy of Closed Head Injuries (clinical paper).

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## A P P E N D I X .



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## Tables.

The influence of test procedures (injections or ihhalations) and their modification by experimental cerebral unilateral edema, as produced by three varied techniques is shown in table 1.

| Testsubstance used | control | intracarotid injection of $H_2O$ | rapid deflation technique | temporary carotid occlusion |
|---|---|---|---|---|
| Acetylcholine | *d | a | a | a |
| Adrenaline | c | a | a | e |
| Aminophylline | c | e | e | e(intracarotid:a) |
| Caffeine | d/c | a | a | e |
| Ergotamine tart. | c | e | e | e |
| n-adrenaline | c | a | a | a/e |
| Papaverine | d | a | a | a |
| Joduron 7o % | d(aft.inj) | e/a | e/a | e/a |
| Pentothal | e | e | e | e |
| Amyl nitrite* | d | a | a | a |
| $CO_2$ | d | a | a | a |
| $N_2$ | d | a | a | a |

d-dilates, c-constricts vessels, e-equivocal effect. a-resp. augmented.
* indicates most reliable for evaluation of tendency to edema .

The settings for capacitance and resistance varied within certain limits. The limits and the values encountered most often are given in table 2. With the values most often encountered, not all traces appeared possible easily ( see text for application, under:discussion) . A=animal values. For comparison, under (P.....) values for patients.

| Settings for | | upper limit | lower limit | most commom |
|---|---|---|---|---|
| Resistance (Ohm) | A | 36o | 2oo | 25o |
| | (P | 21o | 12o | 15o ) |
| Capacitance (nF) | A | 5o | 1oo | 7o |
| | (P | 15 | 7o | 3o and 5o) |

## Legends to Figures.

FIG.1. Animal TO-17,check (A). Production of cerebral edema by temporary occlusion of right carotid artery. Control record before procedure. Left half of figure..paper speed 15 mm/sec;right half of figure..1oo mm/sec.There is only a minimum of difference between the tracings of the REG of the two sides.

FIG.2. Animal TO-17, check (B). 12 hours after temporary occlusion of right carotid artery. The two paper-speeds are reproduced here as in figure one. - Note the much higher amplitude and much steeper inclination of the tracing of the right side as compared to the one on the left side. Lower pulse frequency than in fig.one.

FIG.3. Animal TO-17,check (C). Control record 36 hours after experimental production of cerebral edema by temporary occlusion of right carotid artery. On the slow tracing, it appears, as if the record had only returned to about pre-occlusion level (compare with fig. one). On the fast strip however, it becomes evidentm that there is yet another marked change between the two sides (R and L ), which has taken place. The perfect temporary coincidence of the first peaks ,present in fig.1 and 2 has disappeared and it is very noticeable that the peak of record R appears much later than the one of record L. This difference was measureable as just over o,o4 sec. This is an example of a record as seen with vascular occlusion on the side of the later peak.

FIG.4. Animal TO-19. Record after temporaray occlusion of left carotid artery for 1o seconds and i.v.injection of caffeine (o,1/kg) with no REG-effect and short decrease of blood pressure as effect of caffeine. Reproduction of continuous record. The difference in amplitude between R and L (L higher than right) is due to the production of experimental cerebral edema 2o hours before this recording was taken.

FIG.5. Animal TO-6/13. Record to show effect of intracarotid injection of n-adrenaline on REG after unilateral cerebral edema has been produced. This same injection does not influence neither BP nor REG in the control animal (dose: o,ooooo5 and o,oooo1 /kg intracarotideally). 48 hours after temporaray occlusion of left carotid artery, (A is control) injection of o,oooo1 n-adrenaline /kg produced (B: 1 minute after injection) decrease in amplitude of REG both on the injected and the other side,may be somewhat more so on side not subjected to temporary occlusion of carotid. 1o minutes after injection (record C) pre-injection level is re-established. Under this dose, there is no blood pressure reaction as seen in the femoral artery.Compare with fig.7.

FIG.6. Animal AD-3/35. Recorded after exp.cerebral edema was produced by rapid deflation method, on right side. Effect on REG(control:A) and BP of i.v.injection of aminophylline(3o sec. after inject.:B) and return to normal (almost )pressure after 2 minutes(C). Paper speed: A..1oo mm/sec, B and C.. 3o mm/sec.

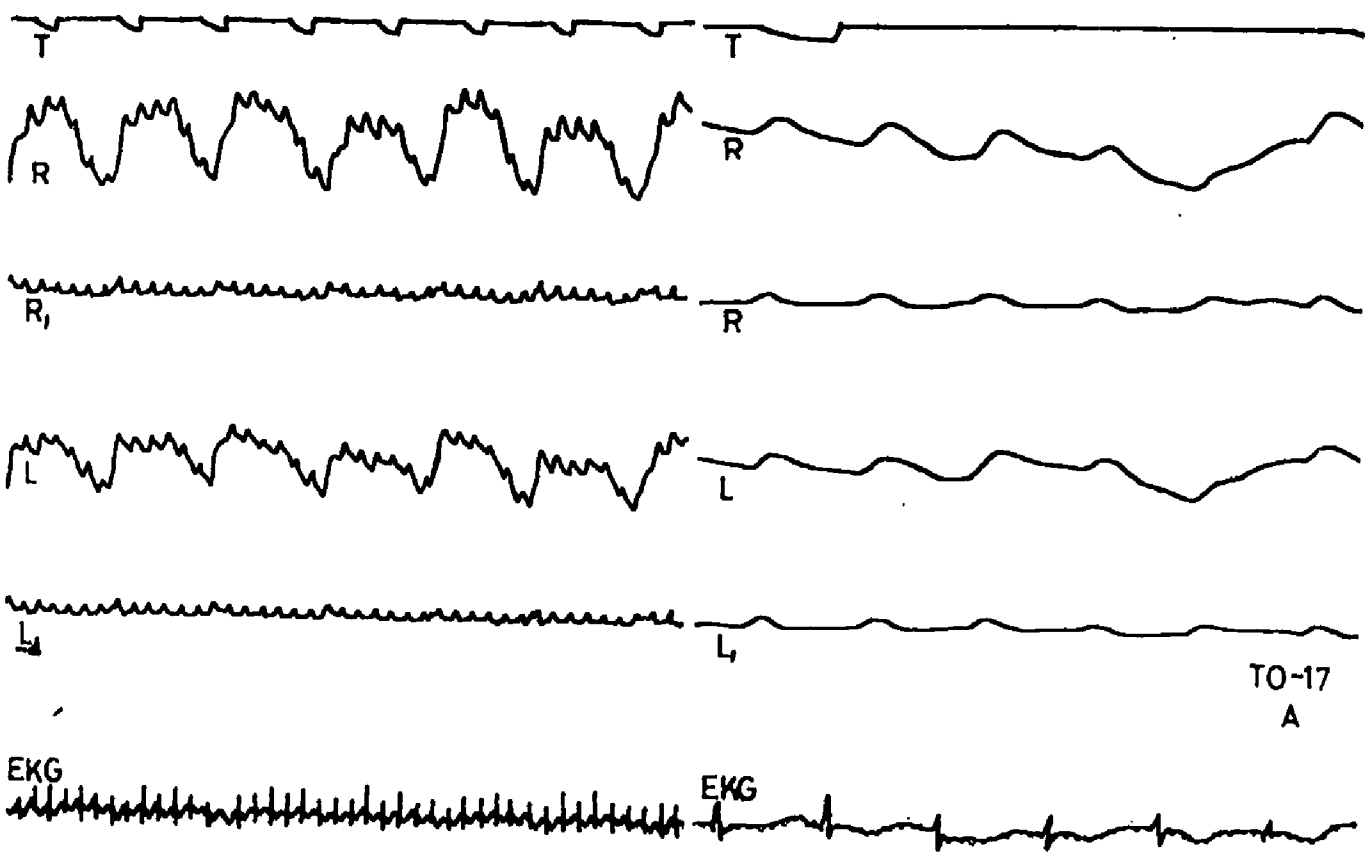
FIG.7. Animal TO-6/24. 11 days after this animal was subjected to temporary occlusion of the left carotid artery, a normal REG-tracing had persisted for 5 days. At this point, a temporary occlusion of the right carotid artery was executed and the record (A) is presented. As usual for experimental cerebral edema, amplitude and may be also a bit the inclination is higher on the experimental-edema side. Paper speed: 1oo mm/sec. 2 days after temporary occlusion, this record was taken and followed by intracarotid(right - sided ) injection of o,ooc1 n-adrenaline. Effect of decrease in amplitude (B) well established, more so on injected side, but also on other side. 2o min.later, pre-injection level of REG is re-established. Compare with fig. 5.

FIG.8. Animal BC-21 (N-4). 24 hours after temporary occlusion of left carotid artery, this tracing before(A),3 min.after (B) and 4 min. after (C) respiration of pure nitrogene (via funnel) in an open system without the removal of exspired $CO_2$ was recorded.The effect on REG recorded is therefore due to either only $N_2$or the combined effect of $N_2$and $CO_2$. The late meximum andthe relative fast return to almost pre-inhalation-level was more frecuently seen with $N_2$ under $CO_2$-absorption. Please note much higher amplitude on side of effect d cerebral experimental edema.

FIG.9. Animal AD-26/ach 17.After production of right sided experimental cerebral edema. Continuous reproduction of REG-and BP-record during and after injection of physiol.NaCl, preceeded by injection of traces of acetylcholine through the same canula. ART=artefact. Very minute cuantities of acetylcholine must still have been present in the canula and effect the BP-drop, which is about 5oo mm/$H_2O$ and the barely visible REG-answer,mostly limited to the right side(edema-side). Paper speed: 15 mm/sec.

FIG.1o. Composite blood pressure recording of BP-response to supplement special observation reported in ATR of R+D 44 7. REG-responses to acetylcholine are prevented or reversed by various anticholinergic drugs. But injection of these substances sometimes - and more often so than not - causes definite blood pressure responses as shown before . . The lines representing pressure recordings are (from top to bottom): Control tracing(C). - Line 2 and 3 are continuous,pressure values given at beginning and end of recording(beginning of 2nd and end of 3rd line : pressure changes observed with an injection(i.v.) of acetylcholine, o,ooo1/kg during the time period marked /_A_/. Line 4 continuous with line 5: anticholinergic (experimental)substance /_D_/ injected preceeding the adetylcholine. No changes except a slight downward drift rather late. Line 6: Injection of anticholinergic alone during the time marked /_D_/ does not show any pressure changes.

Waves suprponed are respiratory in nature. T=time ;one second.
Paper speed was 15 mm / sec throughout.
Pressures given in mm/$H_2O$.


T
T
R
R
R1
R
L
L
L1
L1
TO-17
A
EKG
EKG

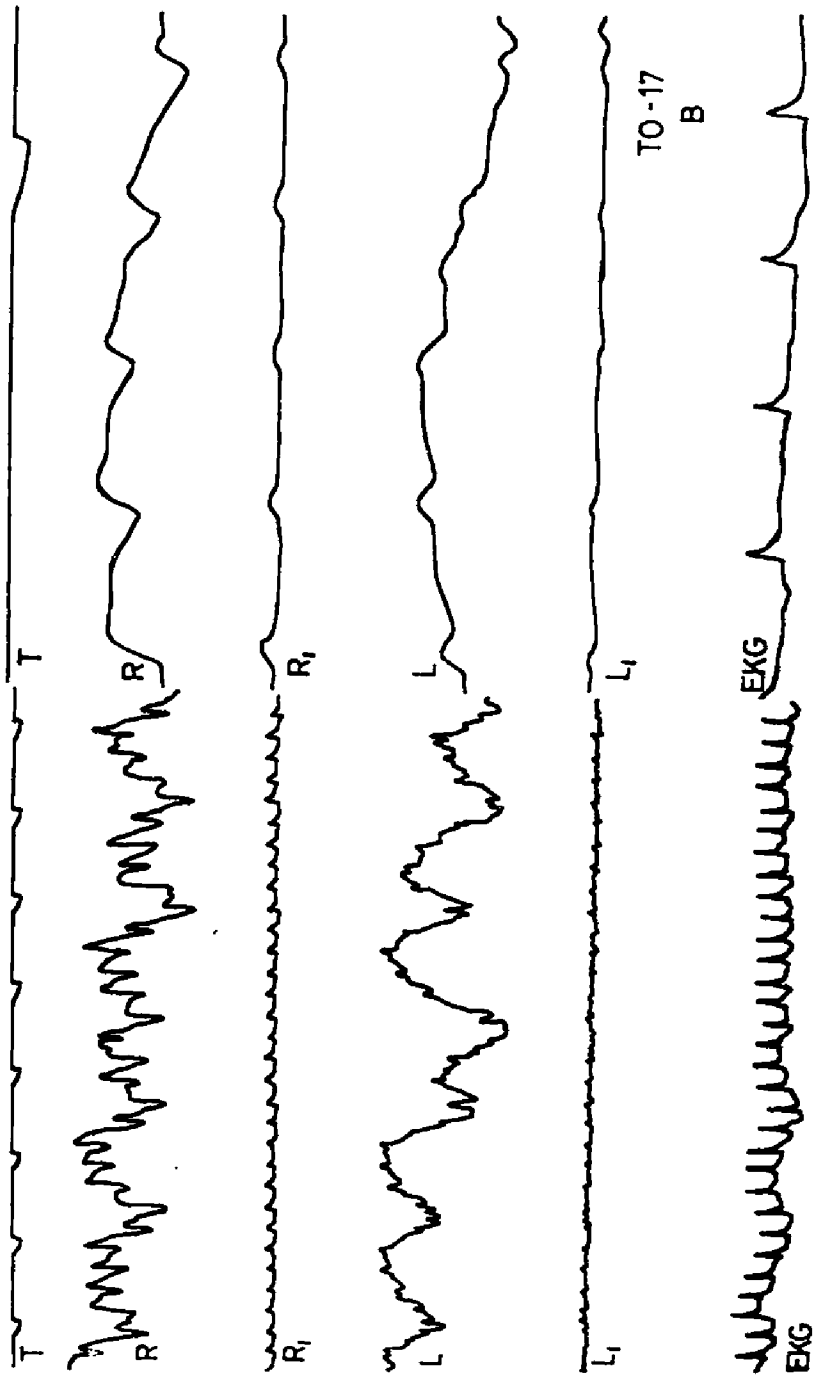



Figure 2 .

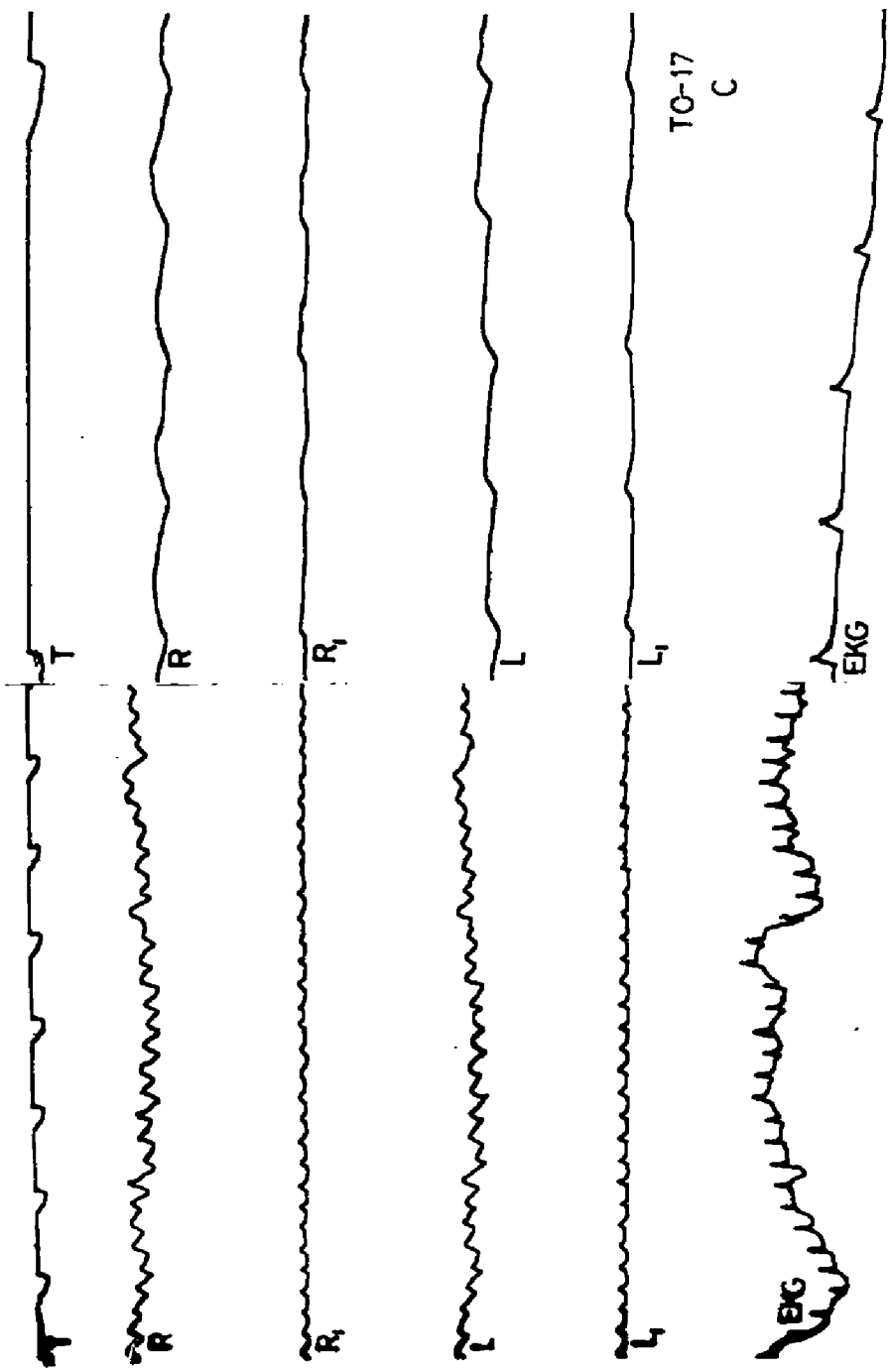



Figure 3 .

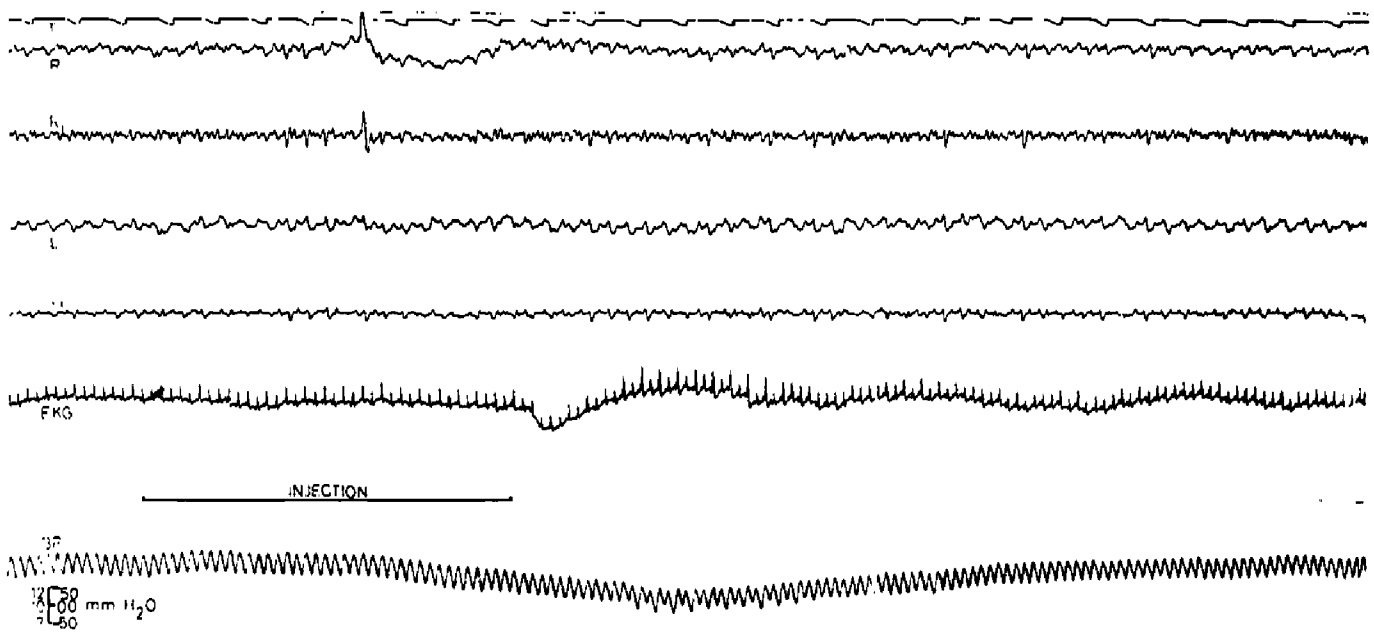



Figure 4 .

Figure 5 .

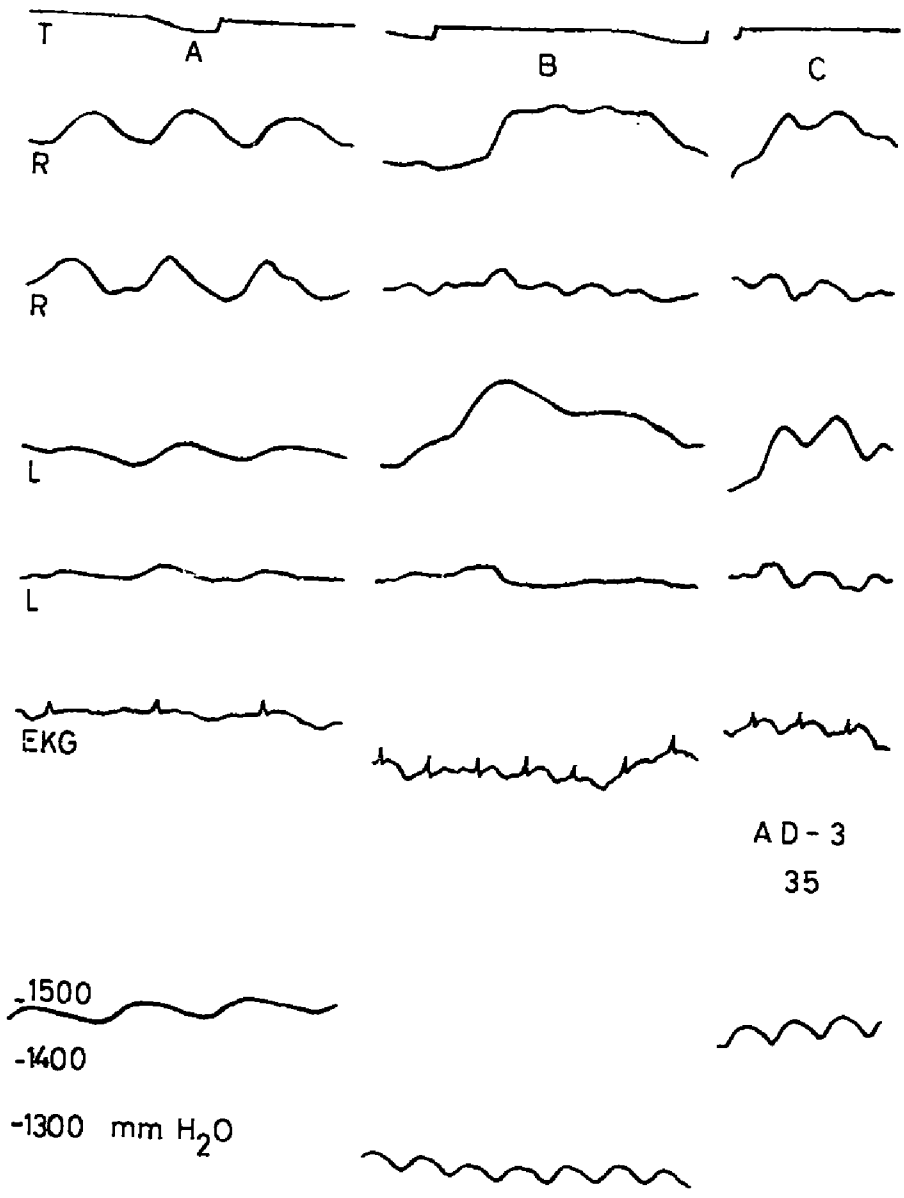



Figure 6 .

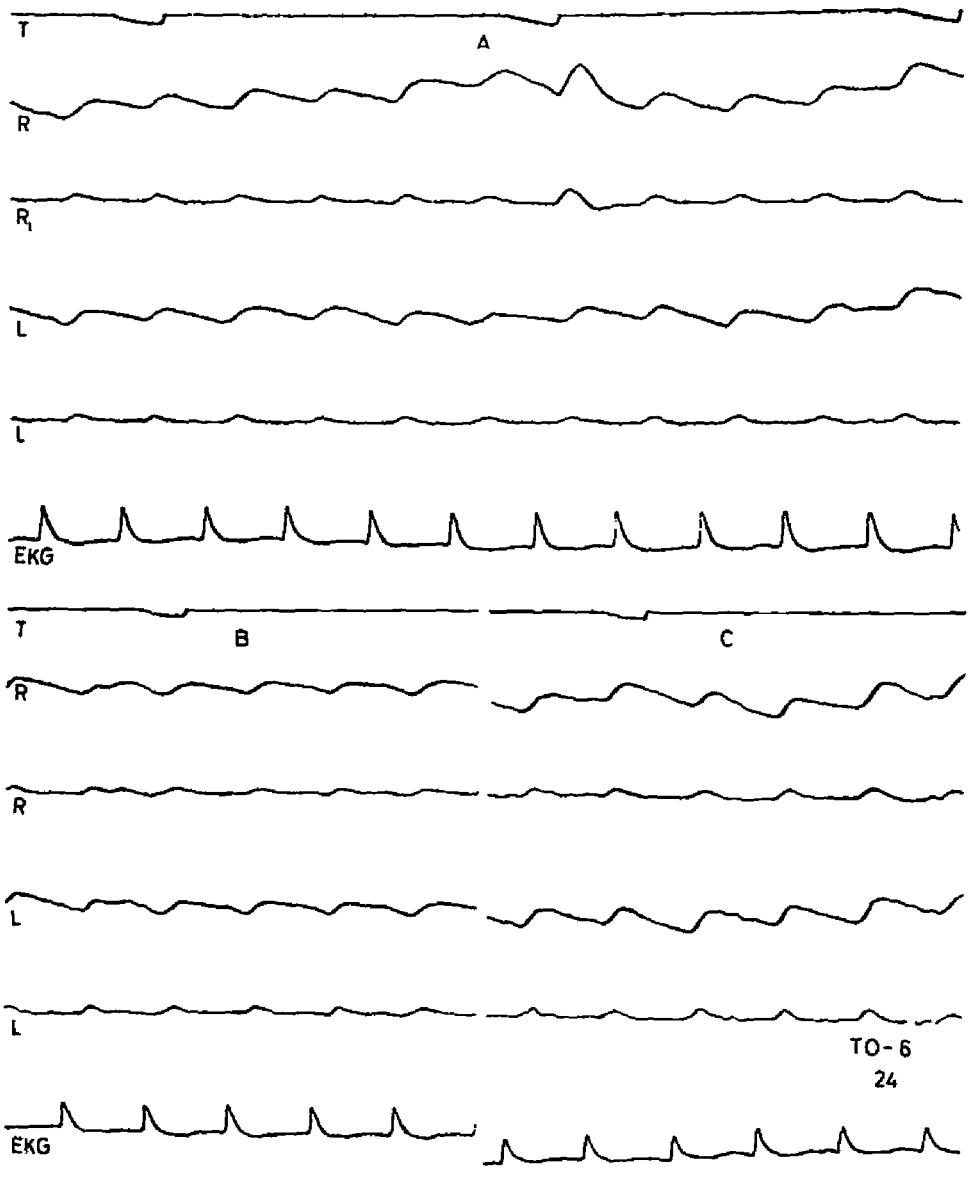



Figure 7 .

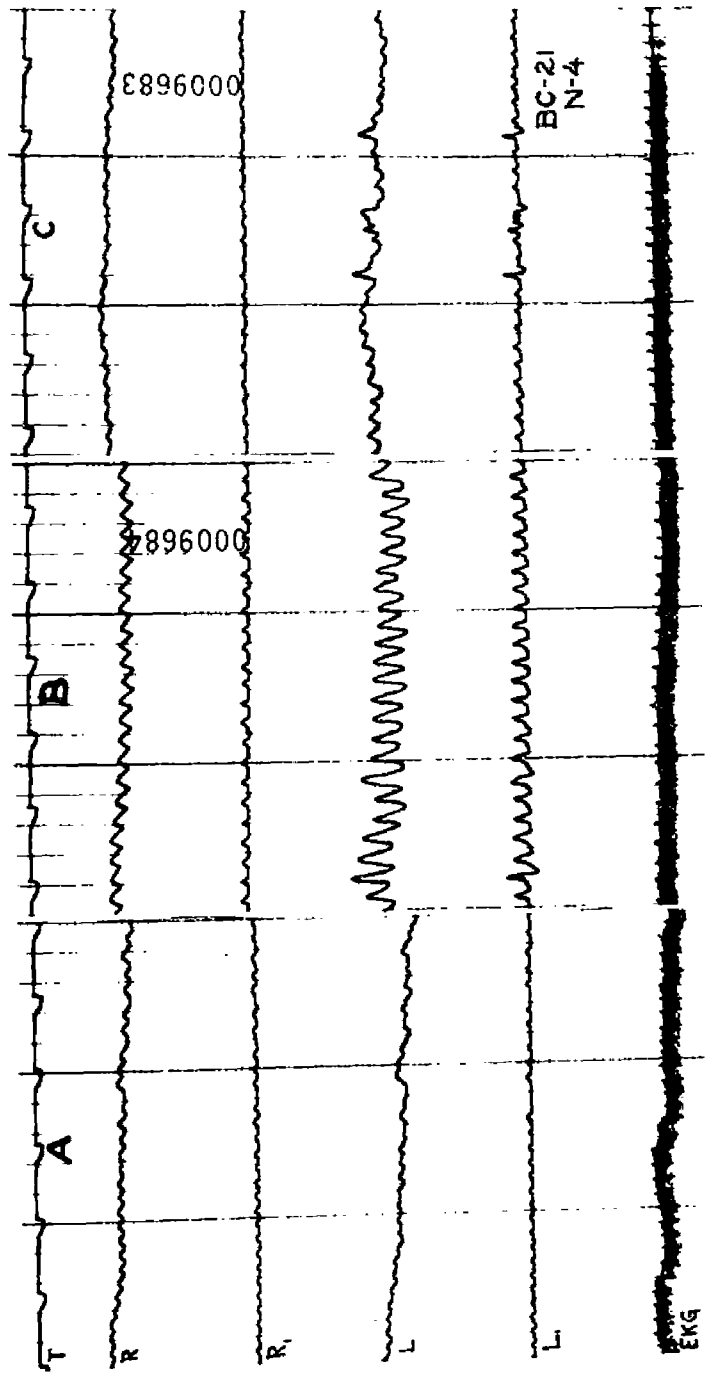



Figure 8

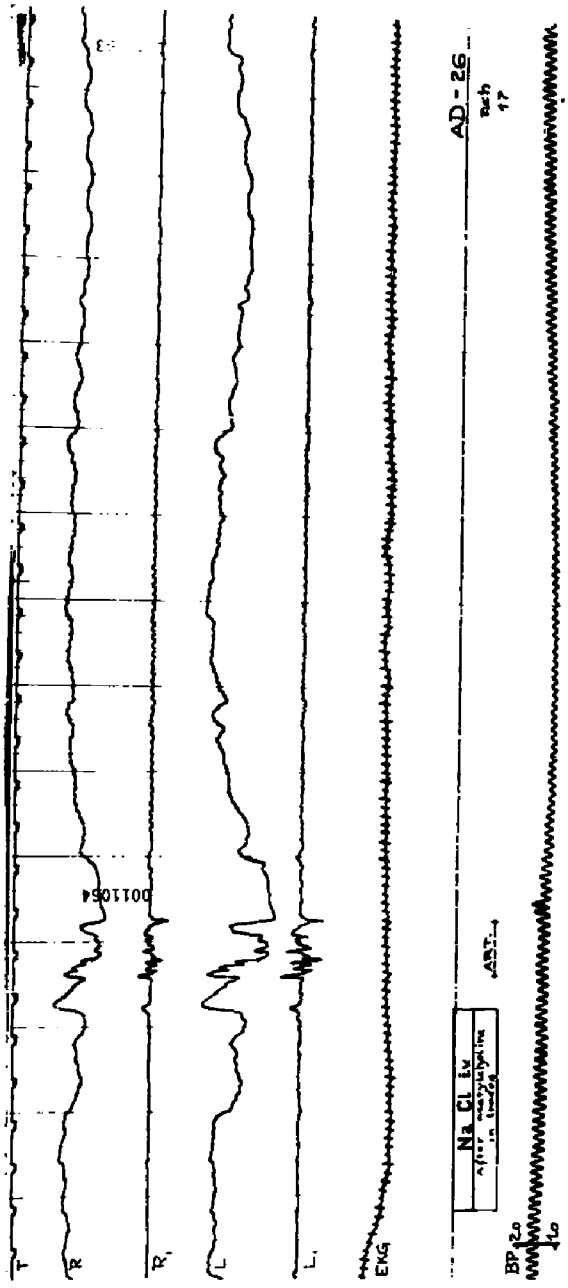



Figure 9 .

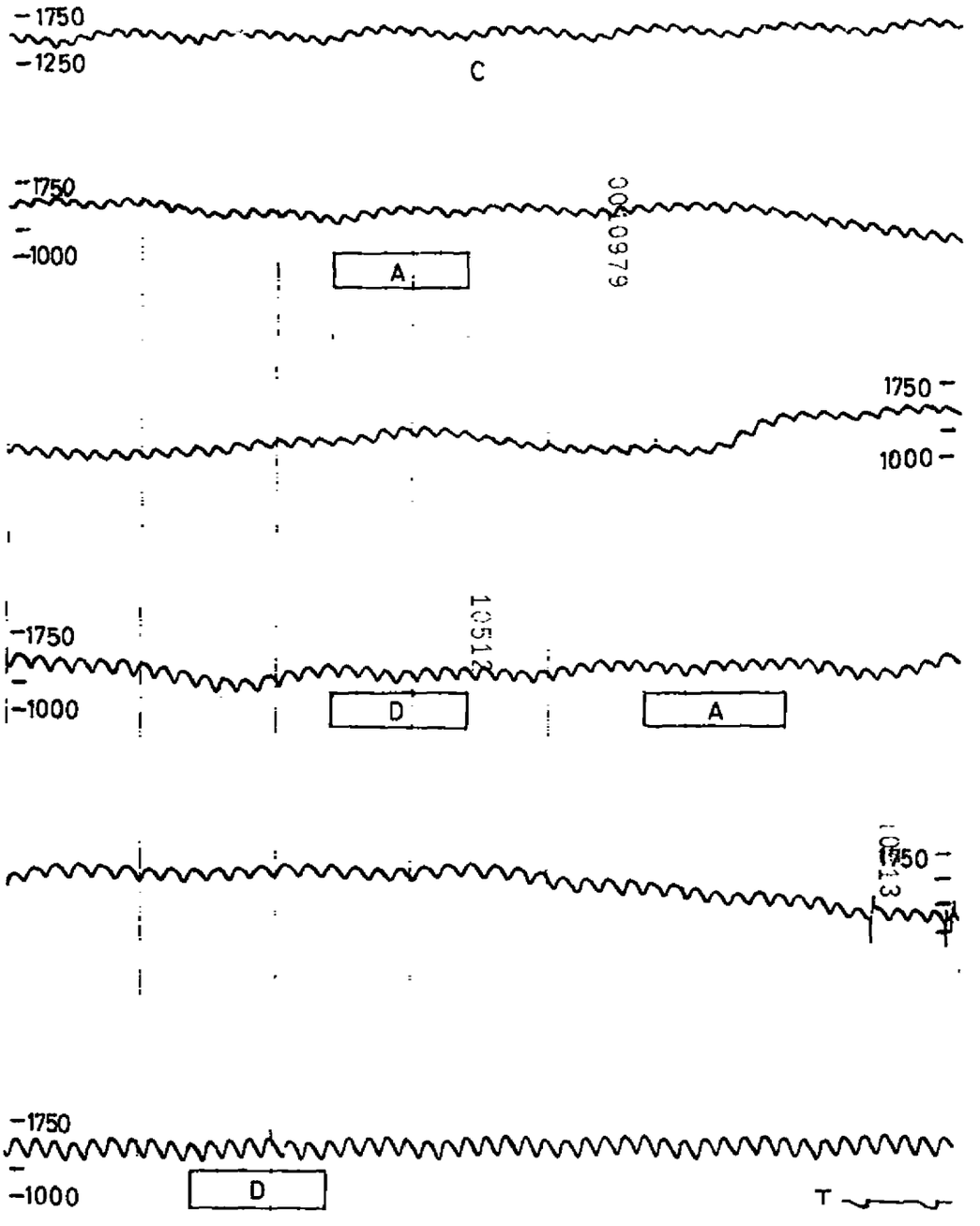



Figure 1c .

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